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Evolution of glycated haemoglobin in adults on growth hormone replacement therapy

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KEYWORDS
Growth hormone;
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Abstract
Objectives: To evaluate the effects of GH replacement therapy (GHR) for 3 years on glycated haemoglobin (HbA_{1c}) and on the presence of dysglycaemia at any time during follow-up in Spanish adult patients with growth hormone deficiency (GHD).
Study design: A retrospective study of 41 patients with GHD was conducted using baseline and long-term data. Changes in HbA_{1c} values during the first 3 years of GHR were studied in both the overall population and patients with or without dysglycaemia during follow-up. Dysglycaemia was defined as FPG $\geq$ 100 mg/dl and/or $HbA_{1c} \geq 5.7\%$.
Results: Mean HbA_{1c} value ($5.4 \pm 0.4\%$ at baseline) increased during the first and second years of GHR (HbA_{1c} $5.5 \pm 0.4\%$, $p = 0.05$, and $5.5 \pm 0.4\%$, $p = 0.006$ respectively). This increase was not maintained during the third year (HbA_{1c} $5.4 \pm 0.3\%$, $p = 0.107$) of GHR. Twenty-eight patients (68.2%) had dysglycaemia during follow-up, 9 of them since baseline. In the 19 patients without baseline dysglycaemia, HbA_{1c} increased during the first year and remained stable in the next 2 years (mean HbA_{1c} $5.2 \pm 0.4\%$ at baseline; $5.5 \pm 0.4\%$ at 1 year, $p < 0.050$; $5.4 \pm 0.4\%$ at 2 years, $p = 0.004$, and $5.4 \pm 0.4\%$ at 3 years, $p = 0.016$). In the 9 patients with baseline dysglycaemia, HbA_{1c} did not significantly change during the 3 years of GHR therapy.
Conclusions: HbA_{1c} values increased during the first 2 years of GHR therapy. In patients with no dysglycaemia before treatment, HbA_{1c} steadily increased over the 3 years. However, it did not change in patients with baseline dysglycaemia.

Abbreviations: BMI, body mass index; DM, diabetes mellitus; FPG, fasting plasma glucose; GHD, growth hormone deficiency; GHR, growth hormone replacement; HbA_{1c}, glycated haemoglobin.

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PALABRAS CLAVE
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disglucemia

Comportamiento de la hemoglobina glicada en adultos con déficit de GH en tratamiento sustitutivo

Resumen
Objetivo: Evaluar, en una cohorte de pacientes españoles con déficit de GH (GHD), el efecto de 3 años de tratamiento sustitutivo con hormona de crecimiento (GHR) sobre la hemoglobina glicada (HbA_{1c}) y la presencia de disglucemia en cualquier momento del seguimiento.
Diseño: Estudio retrospectivo de 41 pacientes con GHD en GHR. Se analizaron los cambios durante los tres primeros años de GHR, en los valores de la HbA_{1c} tanto en la población general como en los subgrupos de pacientes con y sin disglucemia durante el seguimiento. Se definió disglucemia como una glucemia basal $\geq$ 100 mg/dl y/o $HbA_{1c} \geq 5{,}7\%$.
Resultados: La HbA_{1c} media (inicialmente $5{,}4 \pm 0{,}4\%$) aumentó durante el primer y segundo año de GHR (HbA_{1c} $5{,}5 \pm 0{,}4\%$, $p = 0{,}05$ y $5{,}5 \pm 0{,}4\%$, $p = 0{,}006$, respectivamente); esta tendencia no se mantuvo durante el tercer año (HbA_{1c} $5{,}4 \pm 0{,}3\%$, $p = 0{,}107$). Veintiocho pacientes (68,2%) presentaron disglucemia durante el seguimiento, 9 de ellos desde el inicio del seguimiento. En los 19 pacientes sin disglucemia basal, la HbA_{1c} se incrementó durante el primer año, permaneciendo estable durante los siguientes dos años (HbA1c media basal $5{,}2 \pm 0{,}4\%$, 1er año $5{,}5 \pm 0{,}4\%$, $p < 0{,}050$; 2do año $5{,}4 \pm 0{,}4\%$ $p = 0{,}004$ y 3er año $5{,}4 \pm 0{,}4\%$ $p = 0{,}016$). En los 9 pacientes con disglucemia basal la HbA_{1c} no cambió en forma significativa durante los 3 años de GHR.
Conclusiones: Los valores de HbA_{1c} aumentaron durante los dos primeros años de GHR. En los pacientes sin disglucemia pre-tratamiento la HbA_{1c} presentó un incremento continuo durante los tres años. Sin embargo, no cambió en aquellos pacientes con disglucemia basal.

Introduction

Growth hormone deficiency (GHD) in adults is associated with an adverse metabolic profile, with fat mass gain (especially visceral fat), insulin resistance and type 2 diabetes mellitus (DM2).[1–3] However, GH replacement (GHR) is associated with impaired insulin sensitivity shortly after starting therapy, reflected by increased fasting plasma glucose (FPG) and insulin levels despite reductions in visceral adiposity.[4,5] This impaired insulin sensitivity could be influenced by high doses of GH, especially by its major effects on lipolysis.[6] Many of the early GHD studies in adults used weight-based dosing derived from paediatric practice; therefore, hyperglycaemic side effects were more common.

Available evidence suggests that concerns regarding glucose intolerance in patients receiving long-term GHR have not been substantiated.[7] It has been demonstrated that low-dose GHR over 12 months' period enhances insulin sensitivity, and that GH standard dose (0.48 mg/day) has no effect on glucose metabolism.[8] Other studies have suggested that the increase in FPG do not persist after 6 months of GHR therapy, possibly due to a reduction in abdominal visceral fat.[4,9] In addition, several environmental and lifestyle-related factors could influence glucose abnormalities in patients with GHD.

Glycated haemoglobin (HbA_{1c}) was included in the diagnosis and diabetes risk prediction in 2010.[10] HbA_{1c} range of 5.7–6.4% implies a substantially increased risk of DM. There are few data on the evolution of HbA_{1c} in patients with GHD during GHR therapy,[11–14] and no study has specifically addressed this issue in Spanish patients.

We assessed the development of glucose metabolism disorders and the changes in HbA1c during the first 3 years of GHR in a cohort of Spanish patients with GHR therapy, and examined whether these changes were in range of dysglycaemia.

Materials and methods

Patient population

Data were collected from clinical records of 71 GHD adult Spanish patients who were followed at the Endocrine Department of La Paz University Hospital, in Madrid, Spain, from January 1999 to July 2013. GHD was confirmed through standard stimulation tests like insulin tolerance test or, if it was contraindicated, glucagon stimulation test, or by decreased IGF-I levels for age and sex if multiple pituitary deficiencies were observed. Inclusion criteria for the current study were a confirmed diagnosis of GHD, absence of prior GHR therapy and at least 2 years of follow-up during GHR therapy. Patients who did not complete 2 years of treatment, had an irregular follow-up or had diabetes mellitus (DM) at baseline were excluded.

Although the study was retrospective, all patients were followed on the basis of the same standardised protocol that has been applied in our department for several years. All patients, when appropriate, received hormone replacement therapy in the form of L-thyroxine, hydrocortisone, sex steroids and desmopressin. During the study, the adequacy of hormone replacement therapy was assessed periodically.